

REMARKS

Claims 1-14 are pending and under consideration in the instant application. With the instant Amendment, Claims 1-14 are canceled, new Claims 1-15 are added. For the PTO's convenience, a clean copy of pending Claims 15-29 is attached hereto as Exhibit A.

Applicants expressly reserve the right to pursue any canceled subject matter in one or more related, continuation, divisional or continuation-in-part application(s).

I. THE AMENDMENT OF THE CLAIMS

Claims 1-14 have been canceled without prejudice and new Claims 15-29 are added. New Claims 15-29 are fully supported by the specification and claims as originally filed. For instance, new Claims 15-23 are supported by original Claims 1-8 and by the specification, for example, at page 2, line 25, through page 3, line 21. New Claims 24-26 are supported, for example, by original Claims 9-11, by the specification at page 7, line 21, through page 8, line 10, and at Example 1. New Claims 27-29 are supported by original Claims 12-14 and by the specification, for example, at page 8, lines 12-13, and at Examples 2 and 5.

As the amendments to the claims are fully supported by the specification and claims as originally filed, they do not constitute new matter. Entry thereof is therefore respectfully requested.

II. PRIORITY

Applicants submit herewith a certified copy of European Patent Application No. 00105155.6, filed March 11, 2000. Applicants submit that the instant application has the benefit of priority under 35 U.S.C. § 119 of European Patent Application No. 00105155.6, filed March 11, 2000.

III. THE REJECTIONS UNDER 35 U.S.C. § 101 and 35 U.S.C. § 112

Original Claims 1, 3 and 6-9 stand rejected as allegedly being indefinite. The PTO asserts that the term "thermostable" is indefinite. Applicants submit that one of skill in the art would readily understand the meaning of the term "thermostable" given the teaching of the specification and the knowledge in the art of polymerases. Nevertheless, in order to expedite prosecution and secure allowance of the claims, Applicants have canceled original Claims 1, 3 and 6-9 thereby rendering the rejection of those claims moot. Applicants submit

that new Claims 15-29 do not recite the term “thermostable” and meet the requirements of 35 U.S.C. § 112.

Original Claims 3, 5 and 12 stand rejected as allegedly reciting a limitation with insufficient antecedent basis. With the instant Amendment, Applicants have canceled original Claims 3, 5 and 12 thereby rendering the rejection moot. Applicants submit that new Claims 15-29 have proper antecedent basis and meet the requirements of 35 U.S.C. § 112.

Original Claims 13 and 14 stand rejected under 35 U.S.C. § 101 and 35 U.S.C. § 112 for allegedly reciting a use without setting forth any steps. With the instant Amendment, Applicants have canceled original Claims 13 and 14 thereby rendering the rejection moot. Applicants submit that new process Claims 17-29 recite steps and meet the requirements for patentability under 35 U.S.C. § 101 and 35 U.S.C. § 112.

Applicants respectfully request that the rejections under 35 U.S.C. § 102 and 35 U.S.C. § 112 be withdrawn.

IV. THE REJECTION UNDER 35 U.S.C. § 102

A. The Rejections of Claims 1-5 and 9-13

Original Claims 1-5 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Pisani *et al.*, 1998, Biochemistry 37:15005-15012 (“Pisani”). Original Claims 1-5 and 9-13 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Truniger *et al.*, 1999, J. Mol. Biol. 286:57-69 (“Truniger 1998”). Original Claims 1-5 and 9-13 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Truniger *et al.*, 1996, EMBO 15:3430-3441 (“Truniger 1996”). Since original Claim 1-5 and 9-13 have been canceled with the instant Amendment, the rejections of these claims are moot. Applicants submit that new Claims 15-29 meet the requirements for patentability under 35 U.S.C. § 102.

The standard for anticipation under 35 U.S.C. § 102 is strict identity. Anticipation under § 102 can only be established by a single prior art reference that teaches each and every element of the claimed invention. *Structural Rubber Products Co. v. Park Rubber Co.* 223 USPQ 1264 (1984).

Claim 15 recites, *inter alia*, a mutant polymerase wherein the wild-type form of the mutant polymerase has at least 80 % amino acid homology to SEQ ID NO:34, and Claims 16-29 depend from Claim 15. SEQ ID NO:34 is a B-type DNA polymerase from the Euryarchaeon *Thermococcus aggregans*. Pisani, Truniger 1998 and Truniger 1996 do not

teach or suggest each and every element of Claim 15 because they do not teach any polymerase that has 80 % amino acid homology to SEQ ID NO:34.

Pisani teaches various mutant polymerases from the species *Sulfolobus solfataricus*. Since the B-type polymerase from the species *Sulfolobus solfataricus* displays less than 50 % amino acid homology to SEQ ID NO:34, Pisani cannot teach or suggest any polymerase that has at least 80 % amino acid homology to SEQ ID NO:34.

Truniger 1999 and Truniger 1996 teach mutant B-type polymerases from the phage ϕ 29. Since the B-type polymerase from phage ϕ 29 displays very little amino acid homology to SEQ ID NO:34, Truniger 1999 and Truniger 1996 cannot teach or suggest any polymerase that has at least 80 % amino acid homology to SEQ ID NO:34.

Since Pisani, Truniger 1999 and Truniger 1996 do not teach a polymerase that has at least 80 % amino acid homology to SEQ ID NO:34, they do not anticipate Claims 15-29. Applicants respectfully request that the rejections under 35 U.S.C. § 102 be withdrawn.

B. The Rejection of Claims 1-14

Original Claims 1-14 stand rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Bohlke *et al.*, 2000 (October 15), Nucleic Acids Research 28:3910-3917 ("Bohlke"). Applicants respectfully traverse this rejection on the ground that Bohlke is not prior art to the instant application.

A printed publication can be prior art under 35 U.S.C. § 102(a) only if it publishes before the invention by an applicant for a patent. *See* 35 U.S.C. § 102(a). Bohlke is not prior art to the instant application under 35 U.S.C. § 102(a) because Bohlke was published after the priority date of the instant application. The instant application claims the benefit of priority under 35 U.S.C. § 119 of European Patent Application No. 00105155.6, filed March 11, 2000, and Bohlke was not published until October 15, 2000. Since Bohlke was published after the priority date of the instant application, Bohlke cannot be prior art under 35 U.S.C. § 102(a). Applicants therefore respectfully request that the rejection under 35 U.S.C. § 102(a) over Bohlke be withdrawn.

V. REJECTION UNDER 35 U.S.C. §103

Original Claims 1-14 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over a combination of Bohlke, Truniger 1996, Pisani in view of Niehaus *et al.*, 1997, Gene 204:153-159 ("Niehaus") and Bordo *et al.*, 1991, J. Mol. Biol. 271:721-729

("Bordo"). Applicants submit that the rejection of original Claims 1-14 is moot since those claims have been canceled with the instant Amendment. Applicants submit that new Claims 15-29 meet the requirements for patentability under 35 U.S.C. § 103(a)

A. The Legal Standard of *Prima Facie* Obviousness

To reject claims in an application under 35 U.S.C. § 103, the Patent Office bears the initial burden of establishing a *prima facie* case of obviousness. *In re Bell*, 26 USPQ2d 1529, 1530 (Fed. Cir. 1993); MPEP § 2142. In the absence of establishing a proper *prima facie* case of obviousness, applicants who comply with the other statutory requirements are entitled to a patent. *In re Oetiker*, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). In order to establish *prima facie* obviousness, three basic criteria must be met.

First, the prior art must provide one of ordinary skill in the art with a suggestion or motivation to modify or combine the teachings of the references relied upon by the PTO to arrive at the claimed invention. When an obviousness determination relies on one reference, there must be suggestion or motivation to modify the teaching of the reference in the manner suggested by the PTO. *In re Grabiak*, 226 USPQ 870 (Fed. Cir. 1985). Alternatively, when an obviousness determination relies on a combination of two or more references, there must be some suggestion or motivation to combine the references. *WMS Gaming Inc. v. International Game Technology*, 51 USPQ2d 1385, 1397 (Fed. Cir. 1999). The suggestion or motivation to combine the references generally arises in the references themselves, but may also be inferred from the nature of the problem or occasionally from the knowledge of those of ordinary skill in the art. *See id.* The mere fact that references could be modified or combined does not render the resultant modification or combination obvious unless the prior art also suggests the desirability of the modification or combination. *In re Mills*, 16 USPQ2d 1430 (Fed. Cir. 1990); MPEP § 2143.01.

Second, the prior art must provide one of ordinary skill in the art with a reasonable expectation of success. Thus, the skilled artisan, in light of the teachings of the prior art, must have a reasonable expectation that the modification or combination suggested by the PTO would succeed. *In re Dow*, 5 USPQ2d 1529, 1531-32 (Fed. Cir. 1988).

Third, the prior art, either alone or in combination, must teach or suggest each and every limitation of the rejected claims. *In re Gartside*, 53 USPQ2d 1769 (Fed. Cir. 2000). The teaching or suggestion to make the claimed invention, as well as the reasonable expectation of success, must come from the prior art, not Applicants' disclosure. *In re Vaeck*,

20 USPQ2d 1438 (Fed. Cir. 1991). If any one of these criteria are not met, *prima facie* obviousness is not established, and Applicants are not required to show new or unanticipated results. *In re Grabiak*, 226 USPQ 870 (Fed. Cir. 1985).

B. New Claims 15-29 are Patentable Over the Cited References

As discussed above, Bohlke is not prior art to the instant application and cannot form the basis of a *prima facie* obviousness rejection of Claims 15-29. The remaining references, Truniger 1996, Pisani, Niehaus and Bordo, are not sufficient to form the basis of a *prima facie* obviousness rejection of Claims 15-29 because they do not teach or suggest each and every element of Claims 15-29.

Claim 15 recites a mutant polymerase wherein the tyrosine of the Y-GG/A amino acid motif of the mutant polymerase is substituted with another amino acid, and wherein the wild-type form of the mutant polymerase has at least 80 % amino acid homology to SEQ ID NO:34. Claims 16-29 depend from Claim 15.

Truniger 1996, Pisani, Niehaus and Bordo, alone or in any combination, do not teach or suggest mutation of the tyrosine residue in the Y-GG/A amino acid motif of a polymerase that has at least 80 % amino acid homology to SEQ ID NO:34. As discussed above, Truniger 1996 and Pisani fail to even teach or suggest any polymerase that at least 80 % amino acid homology to SEQ ID NO:34, much less mutation of such a polymerase. Truniger 1996 and Pisani deal with unrelated polymerases and suggest nothing about mutating a polymerase that at least 80 % amino acid homology to SEQ ID NO:34.

Similarly, Bordo does not teach or suggest a polymerase that at least 80 % amino acid homology to SEQ ID NO:34, or any mutation of such a polymerase. Bordo merely teaches matrices of preferred amino acid exchanges for site-directed mutagenesis based on various sequence alignments of globins, immunoglobins, cytochromes *c*, serine proteases, subtilisins, calcium binding proteins, acid proteases, toxins and virus capsid proteins. Bordo does not even discuss polymerases or mutation of polymerases. Bordo certainly does not teach or suggest a polymerase that at least 80 % amino acid homology to SEQ ID NO:34, and Bordo thus cannot teach or suggest mutation of a polymerase.

Niehaus merely teaches the cloning, expression and characterization of a thermostable DNA polymerase from *Thermococcus* sp. TY. Although the thermostable DNA polymerase from *Thermococcus* sp. TY might have at least 80 % amino acid homology to SEQ ID NO:34, Niehaus does not teach or suggest any mutation of thermostable DNA polymerase

from *Thermococcus* sp. TY. Niehaus simply says nothing about mutation of the polymerase at all.

Moreover, Niehaus in fact teaches away from mutation of the polymerase. Niehaus observes that the polymerase is an attractive candidate for high PCR performance, as noted by the PTO. Niehaus' observation that the wild-type thermostable DNA polymerase from *Thermococcus* sp. TY is an attractive candidate for PCR leaves one of skill in the art no motivation at all to mutate the polymerase. The PTO has provided no motivation for one of skill in the art to mutate Niehaus' polymerase that, in its wild-type form, is an attractive candidate for high PCR performance.

Furthermore, assuming *arguendo* Truniger 1996, Pisani, Niehaus and Bordo somehow suggest mutation of the tyrosine residue of the Y-GG/A motif of Niehaus, the PTO has failed to provide any reasonable expectation of success such a mutation. The PTO has failed to provide any evidence that mutation of the tyrosine residue of Niehaus' DNA polymerase from *Thermococcus* sp. TY would have any activity at all, much less improved polymerase activity. The PTO has merely pointed to mutations in distantly related or unrelated polymerases that retain some activity. The PTO has not provided any evidence that one of skill in the art could expect a mutation of the polymerase newly cloned and characterized in Niehaus to have improved polymerase activity, or retain any activity at all.

Since Bohlke is not prior art and since none of Truniger 1996, Pisani, Niehaus and Bordo, alone or in any combination, teaches or suggests mutating a polymerase that at least 80 % amino acid homology to SEQ ID NO:34 with any motivation or reasonable expectation of success, the PTO's combination of references are not sufficient to establish a *prima facie* case of obviousness Claims 15-29. Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

Applicants submit that Claims 15-29 satisfy all of the criteria for patentability and are in condition for allowance. An early indication of the same and passage of Claims 15-29 to issuance is therefore kindly solicited.

No fees are believed due in connection with this response. However, the Commissioner is authorized to charge all required fees, fees under 37 CFR § 1.17 and all

required extension of time fees, or credit any overpayment, to Pennie & Edmonds U.S.
Deposit Account No. 16-1150.

Respectfully submitted,

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Enclosure (Exhibit A)



EXHIBIT A
PENDING CLAIMS AFTER ENTRY OF INSTANT AMENDMENT

15. A mutant polymerase comprising a Y-GG/A amino acid motif between an N-terminal 3'-5' exonuclease domain and a C-terminal polymerase domain wherein the tyrosine of the Y-GG/A amino acid motif is substituted with another amino acid, and wherein the wild-type form of the mutant polymerase has at least 80 % amino acid homology to SEQ ID NO:34.
16. The mutant polymerase of Claim 15 that is suitable for polynucleotide amplification.
17. The mutant polymerase of Claim 15 wherein the wild-type form of the mutant polymerase is obtainable from Euryarchaea.
18. The mutant polymerase of Claim 15 wherein the wild-type form of the mutant polymerase is obtainable from *Thermococcus aggregans*.
19. The mutant polymerase of Claim 15 wherein the wild-type form of the mutant polymerase is SEQ ID NO:34.
20. The mutant polymerase of Claim 15 wherein the tyrosine of the Y-GG/A amino acid motif is substituted with an amino acid with an aromatic side chain.
21. The mutant polymerase of Claim 20 wherein the tyrosine of the Y-GG/A amino acid motif is substituted with a phenylalanine, a tryptophan or a histidine.
22. The mutant polymerase of Claim 15 wherein the tyrosine of the Y-GG/A amino acid motif is substituted with an amino acid with a hydrophilic side chain.
23. The mutant polymerase of Claim 22 wherein the tyrosine of the Y-GG/A amino acid motif is substituted with an asparagine or a serine.
24. A DNA encoding the mutant polymerase of Claim 15.

25. A vector comprising the DNA of Claim 24.
26. ^{isolated} A host cell comprising the DNA of Claim 24 or the vector of Claim 25.
27. A process for obtaining a mutant polymerase comprising purification of the mutant polymerase from the host cell of Claim 26.
28. A process for synthesizing nucleic acids, comprising contacting the mutant polymerase of Claim 15 with nucleotides, a primer and a polynucleotide template under conditions suitable for elongation of the primer.
29. A process for polynucleotide amplification comprising contacting the mutant polymerase of Claim 15 with nucleotides, primers and a polynucleotide template under conditions suitable for amplification of the polynucleotide.